Brit. J. vener. Dis. (1965), **41**, 117.

CLINICAL ASPECTS OF PENICILLIN FAILURE IN GONORRHOEA*

BY

PAMELA M. WRAY

Royal Hospital, Sheffield

The penicillin dosage for acute urethral gonorrhoea in males varies not only in different parts of the world but also in different parts of the country. There is a spiral of increasing one-shot dosage which is set in motion by an increasing failure rate. Before 1957 the dose was usually restricted to 0·3 mega units of an aqueous or oily suspension of procaine penicillin or of procaine penicillin in oil with 2 per cent. aluminium monostearate (PAM). Today 2·4 mega units is a not unusual dose.

In Sheffield we have not yet arrived at this exalted twist of the spiral. In 1960 the routine dose was increased to 0·6 mega units of aqueous procaine penicillin, but with a relapse rate which is again rising it behoves us to assess the relapses from the clinical and laboratory point of view. A correlation between increasing failure rate and decreasing sensitivity of the gonococcus to penicillin has been reported from various centres (WHO, 1963), but clinical appraisal of the relapses has been somewhat neglected. The study of extended or well-established urethritis is the clinical no-man's-land into which I wish to venture.

Material

This survey comprises 228 cases of acute gonococcal urethritis in males treated with 0·3 mega units of PAM in 1959, and 825 treated with 0·6 mega units of aqueous procaine penicillin in the years 1961, 1962, and 1963. The year 1960 was a confused one therapeutically speaking and has been omitted. The following cases from the total material available in Sheffield have been excluded: patients treated with penicillin in doses other than those stated, or with drugs other than penicillin; cases of rectal or ophthalmic gonorrhoea; cases of complicated infection; and cases treated elsewhere than at the Royal Hospital and Royal Infirmary in Sheffield.

Two facets which might pinpoint the potential failure have been studied. The first was the finding of posterior urethritis, and was diagnosed where the second specimen of the two-glass urine test was other than clear at the time of diagnosis. The second was the duration of symptoms as recorded at the first visit—less than three and four days respectively, and longer than six and seven days respectively.

Failure is defined as partial or complete lack of response to treatment. Relapse is defined as recurrence of gonococcal discharge within fourteen days of treatment in the absence of a history of further exposure. Failure and relapse have been classified together in the tables.

Results

Table I shows the yearly number of cases included in the survey, the proportion of the total Sheffield cases of acute gonorrhoea in the male which they represent, the relapse rate in the survey cases and the number of such relapses. The dose of penicillin in 1959 was 0·3 mega units of PAM and in 1961, 1962, and 1963 it was 0·6 mega units of aqueous procaine penicillin. The relapse rate was markedly reduced in 1961 after the introduction of the 0·6

TABLE I

RELAPSE RATE OF CASES UNDER SURVEY

Year	No. of Cases	Per cent. of Sheffield Figure	Relapse Rate	
			Per cent.	Cases
1959	228	82·6	16·2	37
1961	309	88·8	3·9	12
1962	324	94·7	5·8	19
1963	192	78·7	10·4	20

* Short paper read to MSSVD on March 20, 1964.

mega unit régime in 1960. Since 1961, however, it is again on the increase.

Table II shows the incidence of posterior urethritis in patients treated both successfully and unsuccessfully at the first visit. The overall incidence of posterior urethritis is little different in the cases which relapse than in those responding. Eighteen of the 88 patients who relapsed (20·4 per cent.) and 177 of 965 successes (18·3 per cent.) had an infection which extended to the posterior urethra. The year-by-year assessment shows the incidence of posterior urethritis among the relapses to be sometimes higher and sometimes lower than among the successes. There were a number of cases in which no second specimen of urine was available. The proportion of such cases amongst the relapses was similar to that amongst the successes, and since neither the order nor the trend is influenced by these omissions a "corrected" incidence rate is not included in the table.

TABLE II

INCIDENCE OF POSTERIOR URETHRITIS IN SURVEY CASES

Year	Incidence in Relapses (Per cent.)	Incidence in Successes (Per cent.)
1959	32·4	28·3
1961	8·3	20·2
1962	21·0	13·1
1963	5·0	13·4
Overall	20·4	18·3

Table III compares the duration of symptoms in the relapses and the successes. The percentages of patients with symptoms for 2 days and 3 days or less, for 7 and 8 days or more, are tabulated year by year and *in toto*. The proportion of the relapses in which the duration of symptoms is not known differs from the proportion of the successes. Therefore, in this table the total number of failures is 77 and successes 878. Overall, 33·7 per cent. of the relapses and 42·1 per cent. of the successes had symptoms for less than 3 days, whilst 51·9 per cent. of the relapses and 65 per cent. of the successes had symptoms for less than 4 days. On the other hand, 29·8 per cent. of the relapses, but only 16 per cent. of the successes, had complained for more than 6 days, and 16·8 per cent. of the relapses, but only 8·8 per cent. of the successes, for more than 7 days. Except for 1961 there is consistently a higher proportion of the successes in those with a short duration of symptoms and a higher proportion of the relapses in those with a longer duration of symptoms. The year 1961 is interesting from the point of view of the association of the low relapse rate. In this year there was very little difference between the failures and the successes so far as the duration of symptoms is concerned. In the years 1962 and 1963 when the relapse rate was rising, the duration of symptoms in the relapses greatly exceeded the duration in the successes; the difference is most marked where symptoms were present for 6 days and more.

Discussion

The difficulty of differentiating between relapse and re-infection is too well known to be laboured; the criteria for relapses previously described have been strictly followed. The smallness of the number of relapses (only 88 in all) must of necessity restrict the validity of the investigation. The purpose of the investigation was to see whether relapse in acute gonococcal urethritis in the male could be foreseen on clinical grounds. It would seem that the co-existence of posterior urethritis is *not* more common in the failures than in the successes.

Prolonged duration of infection, however, *is* commoner in the relapses than in the successes, particularly in more recent years. In view of this finding it is possible that treatment for acute gonorrhoea in the male of comparatively long standing should be more intensive than for that of short duration.

TABLE III

COMPARISON OF DURATION OF SYMPTOMS IN RELAPSES AND SUCCESSES

Year	Duration of Symptoms							
	Less than 3 Days		Less than 4 Days		More than 6 Days		More than 7 Days	
	Relapse (per cent.)	Success (per cent.)	Relapse (per cent.)	Success (per cent.)	Relapse (per cent.)	Success (per cent.)	Relapse (per cent.)	Success (per cent.)
1959	40·6	45·9	56·2	69·1	21·9	17·0	12·5	8·8
1961	36·4	38·5	63·6	60·8	18·2	16·0	9·1	8·0
1962	31·2	45·8	56·2	68·6	43·7	14·7	31·2	8·0
1963	22·2	38·3	33·3	61·6	38·8	17·6	16·6	11·3
Overall	33·7	42·1	51·9	65·0	29·8	16·0	16·8	8·8

Summary

(1) A clinical review of the failures and relapses in 228 cases of acute gonorrhoea in the male, treated in 1959 with 0·3 mega units of PAM, and 825 cases treated in 1961–3 with 0·6 mega units of aqueous procaine penicillin, has been made.

(2) The incidence of posterior urethritis was similar in patients successfully treated (18·3 per cent.) and in failures (20·4 per cent.).

(3) Prolonged duration of symptoms, *i.e.*, more than six or seven days, was almost twice as frequently associated with failure as with success. A tendency in this direction was a constant feature for each and every year studied. It has been more marked in the last two years when the overall clinical failure rate has risen.

(4) It is suggested that whatever routine treatment is chosen for acute gonococcal urethritis in the male, special consideration for the case that is neither early acute nor yet complicated may be helpful in reducing the failure–relapse rate.

I thank Dr R. S. Morton for his help in compiling this paper.

REFERENCE

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Aspects cliniques des échecs du traitement par la pénicilline dans la gonococcie

RÉSUMÉ

(1) On passe en revue les observations cliniques des cas d'échecs et de rechutes, survenus chez 228 hommes atteints de gonorrhée aiguë, traités par 0,3 méga-unités de PAM en 1959, et 825 cas traités en 1961–63 par 0,6 méga-unités de pénicilline procaïne en suspension aqueuse.

(2) La proportion des cas d'urètrite postérieure fut semblable parmi les malades traités avec succès (18,3%) et les échecs (20,4%).

(3) On remarqua qu'en cas d'échec, des symptômes d'une durée de 6 ou 7 jours furent deux fois plus fréquents qu'en cas de succès. Cette tendance se répéta dans toutes les années étudiées et fut plus accentuée ces deux dernières années pour lesquelles le total des échecs a augmenté.

(4) On suggère que, quel que soit le traitement utilisé en cas d'urètrite gonococcique chez l'homme, une attention spéciale soit apportée aux cas qui ne se déclarent pas d'une façon aiguë à un stade précoce, et qui ne sont pas encore compliqués, ceci afin de réduire le taux échec-rechutes.